THEROX™

Downstream® AO System Device Description

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1 Overview

TherOx has developed a focal hyperbaric oxygen technology to treat ischemic myocardial tissue in heart attack patients. This novel focal approach, unlike hyperbaric chambers that rely on full-body exposure to pressurized oxygen gas, creates a liquid solution of hyper-elevated concentrations of oxygen dissolved in sterile saline called *aqueous oxygen* ("AO"), which is then mixed with a patient's arterial blood and delivered directly to the coronary arteries after primary PCI treatment for acute myocardial infarction. The TherOx AO Therapy procedure utilizes three components: a computerized mobile hardware system, a single-use disposable cartridge, and an infusion catheter. The system is a complex electromechanical hardware device that operates and monitors the extracorporeal circuit throughout the procedure. The cartridge has a three-chambered main body that creates AO solution from inputs of hospital-supplied oxygen gas and physiologic saline, and mixes the AO solution with the patient's normoxic arterial blood to create oxygen-enriched hyperoxemic blood. The cartridge has draw tubing to withdraw the patient's blood and return tubing that attaches to the infusion catheter to return the AO-infused blood back to the patient. Together, the cartridge and catheter comprise the blood-contacting extracorporeal circuit. The aim of the treatment is to resuscitate stunned or damaged myocardium, reducing the size of the infarct and thereby improving cardiac function. An introduction to Aqueous Oxygen Therapy is provided herein, followed by detailed descriptions of all three component devices and the principles of operation. A glossary of terms is available in **Section 8**.

2 Introduction: Aqueous Oxygen Therapy

The clinical benefits of hyperbaric medicine are realized in a broad range of treatment modalities, including wound healing, ischemic stroke and global cerebral ischemia, cancer therapy, and acute myocardial infarction (AMI)[1]. A clinical course of hyperbaric oxygen therapy entails full-body pressurization at a facility with a pressurized chamber and staff dedicated to its operation and maintenance. The effectiveness of hyperbaric oxygen therapy in treating AMI has been explored in several pilot studies with encouraging results[2,3,4,5,6]. The documented benefits include improvement in global and

[1] Jain KK (1999). Textbook of Hyperbaric Medicine. Hogrefe and Huber Publishers.
[2] Cameron AJV *et al.* (1966). Haemodynamic and Metabolic Effects of Hyperbaric Oxygen in Myocardial Infarction. *Lancet* **I**: 833 – 837.
[3] Thurston JG *et al.* (1974). A Controlled Investigation into the Effects of Hyperbaric Oxygen on Mortality Following Acute Myocardial Infarction. *Q J Med* **42**:751 – 770.
[4] Swift PC *et al.* (1992). Myocardial Hibernation Identified by Hyperbaric Oxygen Treatment and Echocardiography in Post infarction Patients: Comparison with Exercise Thallium Scintigraphy. *Am Heart J* **124**:1151 – 1158.
[5] Shandling AH *et al.* (1997). Hyperbaric Oxygen and Thrombolysis in Myocardial Infarction: the "Hot MI" Pilot Study. *Am Heart J* **134**:544 – 550.
[6] Sharifi M *et al.* (2003). Reduction in Clinical Restenosis by Hyperbaric Oxygen Therapy: A Year Later. Presented at the Transcatheter Cardiovascular Therapeutics Conference, September 15 – 19, 2003.

regional heart function and metabolic markers, reduced restenosis, as well as reduced mortality rates, particularly in high-risk and cardiogenic shock patients. Despite a history of promising results in small-scale pilot studies, the widespread use and acceptance of hyperbaric oxygen to treat AMI patients is limited. Hyperbaric chambers are physically incompatible with a cardiac catheterization laboratory (CCL), and inhibit access to the patient during the critical early recovery phase.

To overcome these limitations, TherOx has developed a method and device to deliver hyperbaric levels of dissolved oxygen directly to the heart after acute myocardial infarction. The procedure follows the successful administration of reperfusion therapy by means of percutaneous coronary intervention (PCI) with stenting. The device fits into the treatment regimen and space limitations of the CCL. The apparatus for AO Therapy is shown in **Figure 1**. The apparatus (equipment) includes a hardware device called the Downstream AO System ("AO System") and two single-use disposable devices: the Downstream AO Cartridge ("AO Cartridge") and the [redacted]nfusion Catheter ([redacted]. The AO Cartridge is loaded into the AO System ~~by a healthcare~~ professional (user). The cartridge is connected to the patient by a tubing set that connects to an arterial sheath on the draw side and to the infusion catheter on the return side. The infusion catheter is placed over a guidewire through a guide catheter into the coronary artery by an interventional cardiologist (physician).

[redacted]

Figure 1. Equipment for AO Therapy

The method is conceptually simple:

- Hospital-supplied oxygen gas is dissolved in physiologic saline under high pressure; the resultant highly oxygenated solution is called "Aqueous Oxygen" or "AO" solution.
- AO solution at a flow rate of 3 ml/min is combined with the patient's own arterial blood at 72 ml/min in an extracorporeal circuit to create hyperoxemic blood having an elevated pO_2 level of 760 – 1000 mmHg (equivalent effect of 1.0 – 1.3 ATA hyperbaric treatment locally).
- Hyperoxemic blood is pumped at a rate of 75 ml/min into the revascularized coronary artery via infusion catheter for ninety minutes; existing patient connections, including the femoral introducer sheath and guide catheter, are used for blood withdrawal and coronary access.

The novel concept of creating highly concentrated AO solution and combining it with arterial blood serves as a means of providing focal hyperbaric oxygen therapy. [redacted] The one-time 90-minute procedure requires less than [redacted] of additional fluid loading, and the patient's systemic arterial pO_2 level is not impacted by administration of AO Therapy. The potential benefits of AO Therapy have been examined in pre-clinical and clinical studies, and are the subject of the multi-center study presented in the clinical module of this application.

TherOx conducted a series of animal studies to demonstrate proof of concept for the administration of AO Therapy. Studies performed in collaboration with the [redacted] and Wayne State University show promising results for post-AMI AO Therapy in both canine and porcine models[9,10,11,12]. Key pre-clinical results include improved cardiac

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[7] Brereton GJ *et al.* (1998). Nucleation in Small Capillary Tubes. *Chemical Phys* **230**:253 – 265.
[8] Creech JL *et al.* (2002). Injection of Highly Supersaturated Oxygen Solutions without Nucleation. *J Biomech Eng* **124**:676 – 683.
[9] Spears JR *et al.* (1998). Hyperoxemic Reperfusion with Aqueous Oxygen Improves Left Ventricular Function and Microvascular Flow in the Postischemic Canine Myocardium. *J Am Coll Cardiol* **31**:Abstr Suppl A: 449A (1185 – 127).
[10] Kantor B *et al.* (1998). Coronary Reperfusion with Aqueous Oxygen Improves Left Ventricular Ejection Fraction and May Reduce Mortality in an Ischemic Porcine Model. *Am J Cardiol* **84**:Abstr Suppl 6A: 86S (TCT-231).
[11] Spears JR *et al.* (2002). Aqueous Oxygen Hyperbaric Reperfusion in a Porcine Model of Myocardial Infarction. *J Invas Cardiol* **14**(4): 160 – 166.

function and smaller infarct size in treated animals compared to non-treated controls. The AMI model used in these research efforts was a reversible balloon occlusion of the LAD coronary artery.

In addition to pre-clinical studies, TherOx has conducted three FDA-sanctioned studies in clinical treatment of AMI patients. The first study was a Phase I pilot effort conducted on twenty-nine patients; study results included promising trend data towards improved left ventricular ejection fraction and wall motion score in AO Therapy-treated subjects[13], and served as a foundation for the AMIHOT multi-center randomized trial. No safety concerns were noted during the pilot study. The AMIHOT study was a 1:1 randomized trial that examined outcomes in AMI subjects treated with AO Therapy following PCI with stenting as compared to a Control group receiving PCI with stenting alone. Study results showed improvement in infarct size reduction, reduced ischemic burden, and left ventricular contractility for patients with anterior wall infarctions treated within six hours of symptom onset, and comparable Major Adverse Cardiac Events (MACE) at 30 days. This promising AMIHOT patient cohort was the target population for the pivotal AMIHOT II study. AMIHOT II examined the safety and effectiveness of AO Therapy for anterior < 6 hr AMI patients, seeking to demonstrate superiority in infarct size reduction with no appreciable increase in 30-day MACE.

3 Indications for Use

The TherOx® Downstream® AO System, Downstream® AO Cartridge, and [redacted]™ Infusion Catheter are indicated for: The preparation and delivery of SuperSaturated Oxygen Therapy (SSO_2 Therapy) to targeted ischemic regions of the patient's coronary vasculature immediately following revascularization by means of percutaneous coronary intervention (PCI) with stenting that has been completed within 6 hours after the onset of anterior acute myocardial infarction (AMI) symptoms.

4 Device Description

The equipment required for AO Therapy includes three components: the re-usable hardware AO System, the single-use disposable AO Cartridge, and the single-use [redacted] Infusion Catheter. These three components work in unison to perform the processes of AO delivery and blood circulation to support hyperoxemic blood delivery. The equipment also implements safety measures consistent with the established requirements for these processes. A detailed description of these three components is provided herein.

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[12] Spears JR *et al.* (2003). Aqueous Oxygen Attenuation of Reperfusion Microvascular Ischemia in a Canine Model of Myocardial Infarction. *ASAIO J* **49**(6): 716 – 720.
[13] Dixon SR *et al.* (2002). Initial Experience with Hyperoxemic Reperfusion after Primary Angioplasty for Acute Myocardial Infarction. *J Am Coll Cardiol* **39**(3): 387 – 392.

4.1 AO System

The AO System is a medical electromechanical device (console) that initiates AO Therapy under user control and supervision, with a user interface to guide the operator through setup and clinical operation. The AO System monitors safety and performance of AO solution production and delivery. The system also monitors safety and performance of AO System parameters associated with the blood fluid path. The AO System is intended to be Mains operated (AC-powered) and stationary, but is also internally powered and has the capability for mobile operation. The system is intended for use in the patient vicinity and for continuous operation; blood flow cannot be paused and restarted during AO Therapy administration. The AO System is non-sterile and does not contact the wetted fluid path. The system weighs 280 lbs and is operated by a standing user. The AO System is operated by trained health care professionals familiar with cardiac catheterization laboratory interventional procedures. The AO System is shown in **Figure 2**.

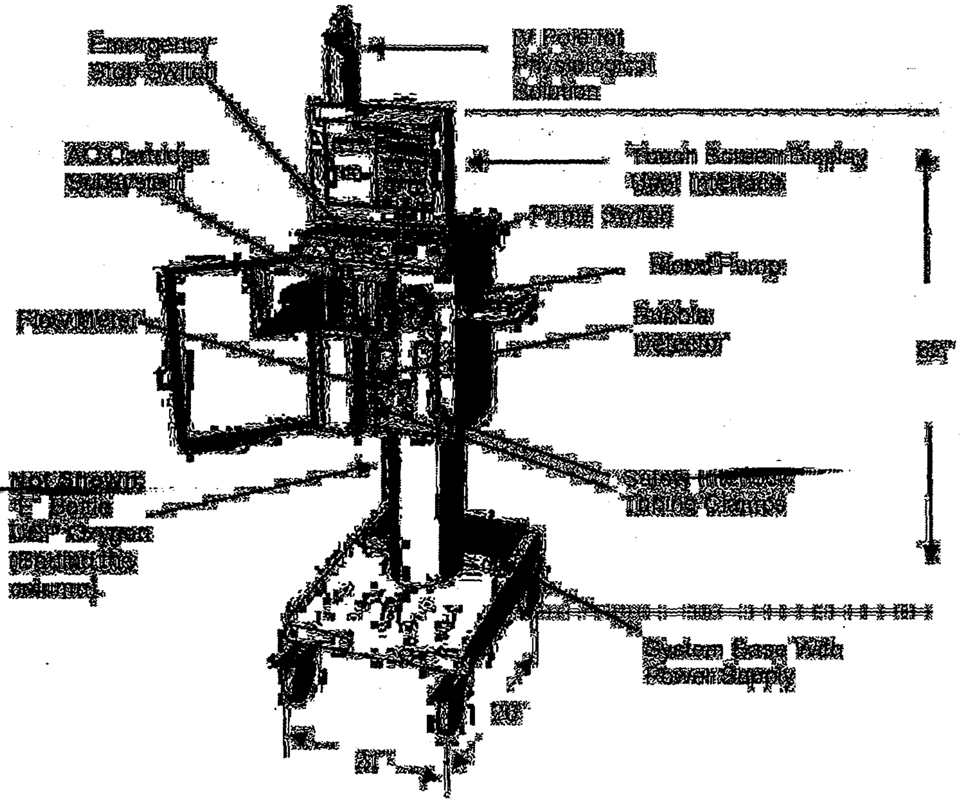

Figure 2. AO System

The AO System chassis consists of a main enclosure mounted upon a system base. The sheet metal main enclosure contains several electronic subsystems and mounting interfaces for these subsystems. A rear service panel provides access to the internal components and has a power switch. The main enclosure also has handles and a front door. A retractable pole for the saline bag is mounted to the main enclosure. The system base supports the main enclosure, contains the power supply and holds the oxygen bottle. The system base has four wheels that fully articulate for system mobility and lock for stability. The following subsystems are integrated into the AO System chassis:

- The AO Cartridge Subsystem (AOCS) houses and operates the AO Cartridge (the AOCS does not contact saline or blood). The AOCS monitors operating parameters within the AO Cartridge. The AOCS controls the flow of oxygen to the cartridge and controls the flow of saline through the cartridge by actuating moving parts within the cartridge. The AO System operating state is controlled by software within the AOCS.

- The Blood Pump Subsystem (Blood Pump) has a fully occlusive peristaltic pump that is loaded with the AO Cartridge draw tubing. The Blood Pump withdraws normoxic arterial blood from the patient's femoral artery and returns hyperoxemic blood via infusion catheter to the coronary arteries.

- The Bubble Detector Subsystem (Bubble Detector) is a custom ultrasound-based device that monitors the return blood flow in the extracorporeal circuit for bubble-free delivery.

- The Safety Interlock Subsystem (Safety Interlock) stops treatment and isolates the AO Cartridge blood path from the patient if a fault condition is detected. The Safety Interlock continuously monitors signals from other subsystems for fault conditions. The Safety Interlock also has a manually operated Emergency Stop switch to disable AO Therapy.

- The User Interface Subsystem (User Interface) has a touch-screen display that guides the user through set-up and clinical operation. The User Interface accepts and initiates user commands, and communicates with the AOCS, Blood Pump, and Bubble Detector subsystems.

- The Oxygen Supply Subsystem (Oxygen Supply) uses a hospital-supplied oxygen E-bottle to provide pressurized oxygen to the AO System. A pressure regulator controls the AO Cartridge oxygen supply pressure.

- The Power Supply Subsystem (Power Supply) provides DC power to the electronic subsystems within the AO System. The Power Supply uses either AC Mains or an internal power supply (battery) as the power source.

The AOCS, Blood Pump, Bubble Detector, and User Interface Subsystems contain software to monitor and control subsystem function. The software architecture and design are described in detail in PMA Module 4.

4.1.1 AO Cartridge Subsystem (AOCS) Detailed Description

[redacted]

The cartridge is inserted into the AOCS by the user. The AOCS has mechanisms that actuate the AO Cartridge piston, needle valves, vent valves, and oxygen supply port, and has electronic sensors for measuring temperature, oxygen pressure, and piston pressure. The AOCS has a printed circuit board (PCB) assembly that contains electrical hardware and software to control the actuators, process the inputs, and communicate to other electrical subsystems. [redacted]

AOCS Housing: The AOCS housing is an anodized aluminum enclosure. The four major parts of the housing assembly are the receiver block, top plate, bottom plate, and door. Pulling the door handle down and forward opens the door when it is unlocked. The user inserts the AO Cartridge into the AOCS housing compartment. Slots in the AOCS housing enable passage of the draw tubing, return tubing and IV tubing. The cartridge is automatically aligned with all mechanical and sensor interfaces within the AOCS housing when the housing door is closed. The pressurized chambers of the disposable AO Cartridge are contained within the AOCS housing.

Door Lock Actuator and Latch Sensor: The door latch mechanism contained in the receiver block of the AOCS housing prevents the door from opening when locked. [redacted]

Cartridge Valve Actuators: The AO Cartridge contains three needle valves and two vent valves that are controlled by the AOCS valve actuators. [redacted]

Three needle valve actuators are contained in the bottom plate of the housing. These three actuators are physically identical [redacted]. The first actuator controls the dilution needle valve; the second actuator controls the flush needle valve; the third actuator controls the AO solution flow needle valve. The needle valves are aligned with the actuators when the cartridge is inserted and the door is closed. Pressure inside the cartridge opens the needle valves when the actuator is in the open position [redacted]

The oxygen vent valve and Blood Mixing Chamber (BMC) vent valve actuators are contained in the top plate of the housing and control the gas venting of the AO Cartridge. The oxygen vent valve releases pressurized oxygen from the cartridge oxygen chamber. The BMC vent valve releases gas in the blood-mixing chamber of the cartridge. The oxygen and BMC vent valves are aligned to the actuators when the cartridge is inserted in the AOCS housing and the door is closed. Gas pressure within the cartridge opens either vent valve when the actuator is in the open position (solenoid energized).

AOCS Oxygen Supply: The oxygen supply mechanical hardware for the AOCS is mounted on the top plate of the AOCS housing. This plate contains an oxygen port that ~~automatically~~ connects and seals to the cartridge oxygen inlet upon placement of the cartridge within the housing. [redacted] This ~~plate also~~ contains tubing and a check valve to prevent gas flow in the reverse direction, from the cartridge back to the oxygen flow valve.

Oxygen Flow Valve: The oxygen flow valve, also mounted to the top plate of the AOCS housing, connects the AOCS to the AO System Oxygen Supply. [redacted]

Oxygen Pressure Transducer: A pressure transducer located within the oxygen supply (upstream from the oxygen port) monitors oxygen pressure in the cartridge. [redacted]

Temperature Sensor: [redacted] This sensor measures the temperature of the AO Cartridge [redacted]

Cartridge Detect Sensor: A reflective sensor mounted in the AOCS housing receiver block detects the presence of an installed cartridge when the door is closed. [redacted]

Level Sensors: Three ultrasonic level sensors mounted in the AOCS housing receiver block monitor liquid levels within the AO Cartridge. These level sensors are: 1) oxygen chamber low level (AO solution level), 2) BMC low level, and 3) BMC high level. Each sensor detects the presence or absence of liquid level within the cartridge at specific locations. [redacted]

[redacted]

Piston Actuator Assembly: The Piston Actuator Assembly is an electromechanical assembly that controls the AO Cartridge piston. The piston allows for fluid transfer of IV bag saline into the cartridge, and for transfer of saline from the piston chamber into the AO Cartridge oxygen chamber to create AO solution. The piston actuator is mounted under the bottom plate of the AOCS housing. [redacted]

The Piston Actuator Assembly includes a load cell that measures compressive force on the piston ram. The load cell provides an analog force signal [redacted] for measurement and conversion to pressure. The [redacted] monitors the pressure to ensure that the operational limit is not exceeded. [redacted]

AOCS PCB: The AOCS PCB receives digital and analog signals from electronic components within the AOCS. The AOCS PCB also monitors Power Supply voltage. The AOCS PCB controls the Piston Actuator and all solenoids within the AOCS. The AOCS PCB operates the fans that ventilate the main enclosure. [redacted]

The AOCS PCB communicates serially with the User Interface and sends/receives digital signals to/from the Safety Interlock.

4.1.2 Blood Pump Subsystem Description

The Blood Pump Subsystem (Blood Pump) withdraws arterial blood from the patient and pumps it through the AO Cartridge and infusion catheter back to the patient. The fully occlusive peristaltic Blood Pump interfaces with the AO Cartridge tubing and thus does not have direct fluid contact. The system user inserts the draw side tubing into the pump head and the return side tubing into the flow probe during system set-up. A modular view of the Blood Pump is shown in **Figure 4.** The Blood Pump PCB provides serial communication to the User Interface and analog and digital signals to the Safety Interlock.

The pump head is coupled to the DC motor mounted inside the Blood Pump enclosure, which is mounted inside the system's main enclosure. The pump head, flow probe and the prime switch are mounted on the front of the main enclosure. [redacted] The Blood Pump operates at a fixed flow rate of 75 ml/min, set by software. The Blood Pump supports the 75 ml/min flow rate set point at hydrodynamic pressures less than or equal to [redacted] The Blood Pump has feedback control with an ultrasonic flow probe in order to maintain a constant reperfusion rate of 75 ml/min. [redacted]

[redacted]

[redacted]

Pump Head: The [redacted] pump head is a three-roller peristaltic pump head mounted on the front of the system main enclosure. The occlusion setting is fully occlusive for the tubing, so the pump head functions as a tubing clamp when stopped. The peristaltic pump features an over-center, cam-actuated mechanism with a handle to facilitate loading of tubing. The pump head shaft is coupled to the Blood Pump DC motor.

[redacted]

Pump Head Detector: The Blood Pump has a sensor to detect if the pump head is closed. [redacted] The pump motor will not turn when the pump head is in the open position.

Flow Probe and Blood Flow PCB: The Flow Probe and Blood Flow PCB provide flow measurement for the return blood path [redacted] The Flow Probe is an ultrasonic transducer mounted on the front of the system main enclosure that clamps onto the return tubing. The system user inserts the return tubing of the AO Cartridge in the Flow Probe and latches the probe door during initial system set-up. [redacted]

Prime Switch: The Blood Pump has a Prime switch mounted to the front of the system main enclosure that the user must press and hold to initiate blood flow into the cartridge and fully prime the tubing and cartridge. [redacted]

Blood Pump Motor and Blood Pump PCB: [redacted] The Blood Pump PCB uses an analog input from the Blood Flow PCB to maintain the flow rate set point, and sends this analog signal to the Safety Interlock. [redacted] The Blood Pump communicates serially with the User Interface and sends/receives digital signals to/from the Safety Interlock.

4.1.3 Bubble Detector Subsystem Description

The Bubble Detector Subsystem (Bubble Detector) has a printed circuit board (PCB) and a transducer that continuously monitors the return blood path for air bubbles. The Bubble Detector PCB has software that counts and calculates the size of each bubble that passes through the return tubing. The Bubble Detector counts individual bubbles as small as 100-µm in diameter. The Bubble Detector PCB software also calculates a cumulative bubble volume. If the cumulative bubble volume reaches 10 µl during the 90-minute treatment, or signal strength is out of range, the Bubble Detector initiates a system shutdown.

The system user inserts the return tubing of the AO Cartridge into the bubble detector transducer and during initial system set-up. [redacted]

[redacted]

[redacted]

Bubble Detector Transducer: [redacted] The ultrasonic transducer clamps onto the return tubing and is physically identical to the flow probe incorporated into the Blood Pump Subsystem. The Bubble Detector transducer is mounted on the front of the main system enclosure directly above the flow probe and has an electrical interface to the Bubble Detector PCB.

Bubble Detector PCB: The Bubble Detector PCB provides the transmit-and-receive functions for the Bubble Detector Transducer. [redacted]

[redacted] The Bubble Detector PCB provides serial communication to the User Interface for accumulated bubble volume, and sends/receives digital signals to/from the Safety Interlock.

4.1.4 Safety Interlock Subsystem Description

The Safety Interlock Subsystem (Safety Interlock) is an electronic assembly with input and output components that can stop AO Therapy administration by clamping the tubing set and signaling other subsystems to stop treatment. [redacted] The Safety Interlock continuously monitors inputs for events that require treatment stoppage. If any of the following conditions occur, the Safety Interlock will stop treatment:

- AOCS, Blood Pump, Bubble Detector, or User Interface fault condition
- User activation of the Emergency Stop switch
- The draw or return tubing pressure transducer signals exceed a maximum signal threshold set on the Safety Interlock
- The flow rate signal from the Blood Pump Subsystem drops below a minimum signal threshold set on the Safety Interlock
- The BMC low level sensor (AOCS) detects low blood level.

Component features of the Safety Interlock Subsystem include the Safety Interlock PCB, Emergency Stop Switch, Pressure Transducer Thresholds, Blood Flow Threshold, and Tubing Clamps.

Emergency Stop Switch: The Emergency Stop Switch is mounted on the front of the system main enclosure and is an input to the Safety Interlock PCB. The switch immediately disables AO Therapy upon manual actuation by the system user regardless of any other monitored input status. The switch latches when pressed and must be manually disengaged.

Pressure Transducer Thresholds: The analog pressure transducer inputs (tubing draw side and BMC) are monitored by the Safety Interlock. Hardware comparators on the Safety Interlock PCB set the threshold for BMC pressure to 2000 mmHg [redacted]; the threshold for draw pressure is –300 mmHg [redacted]. The Safety Interlock has a modular jack on the front of the main enclosure for connection to the AO Cartridge electrical components. During setup, the system user inserts the AO Cartridge modular connector into the modular jack on the front of the system main ~~enclosure.~~

Blood Flow Threshold: the Safety Interlock monitors the analog ~~blood flow~~ rate measurement from the Blood Pump. A hardware comparator on the Safety Interlock PCB is set for a low blood flow rate threshold equal to 50 ml/min [redacted]

~~**Tubing Clamps:** The~~ The Safety Interlock provides the drive electronics to actuate the tubing ~~clamps. Two tubing~~ clamps, the draw tubing clamp ~~and the return~~ tubing clamp, isolate the ~~patient~~ from blood flow in the AO Cartridge in the event ~~of a fault~~ condition. These pinch ~~clamps are~~ normally closed; the system user loads ~~the cartridge tubing~~ into these clamps during initial system set-up. A manual switch on ~~the front of the~~ system main enclosure allows the user to activate (open) both clamps for tubing installation. [redacted]

Safety Interlock PCB: The Safety Interlock PCB provides the logical input and output function to enable or disable AO System operation based on the monitored inputs. [redacted] Each of the four other electrical subsystems (AOCS, Blood Pump, Bubble Detector, and User Interface) provides a logical signal (OK/Fault) to the Safety Interlock; the Safety Interlock returns a logical signal (enable/disable) to each subsystem. The Safety Interlock directly monitors analog signals from the AO Cartridge pressure transducers and the analog blood flow signal from the Blood Pump.

4.1.5 User Interface Subsystem Description

The User Interface Subsystem (User Interface) displays instructions and information to ~~the system user, and~~ provides a means for user input ~~necessary to operate~~ the AO System. ~~The User Interface~~ also displays the running treatment time. ~~The User~~ Interface Subsystem ~~is~~ shown in **Figure 6.**

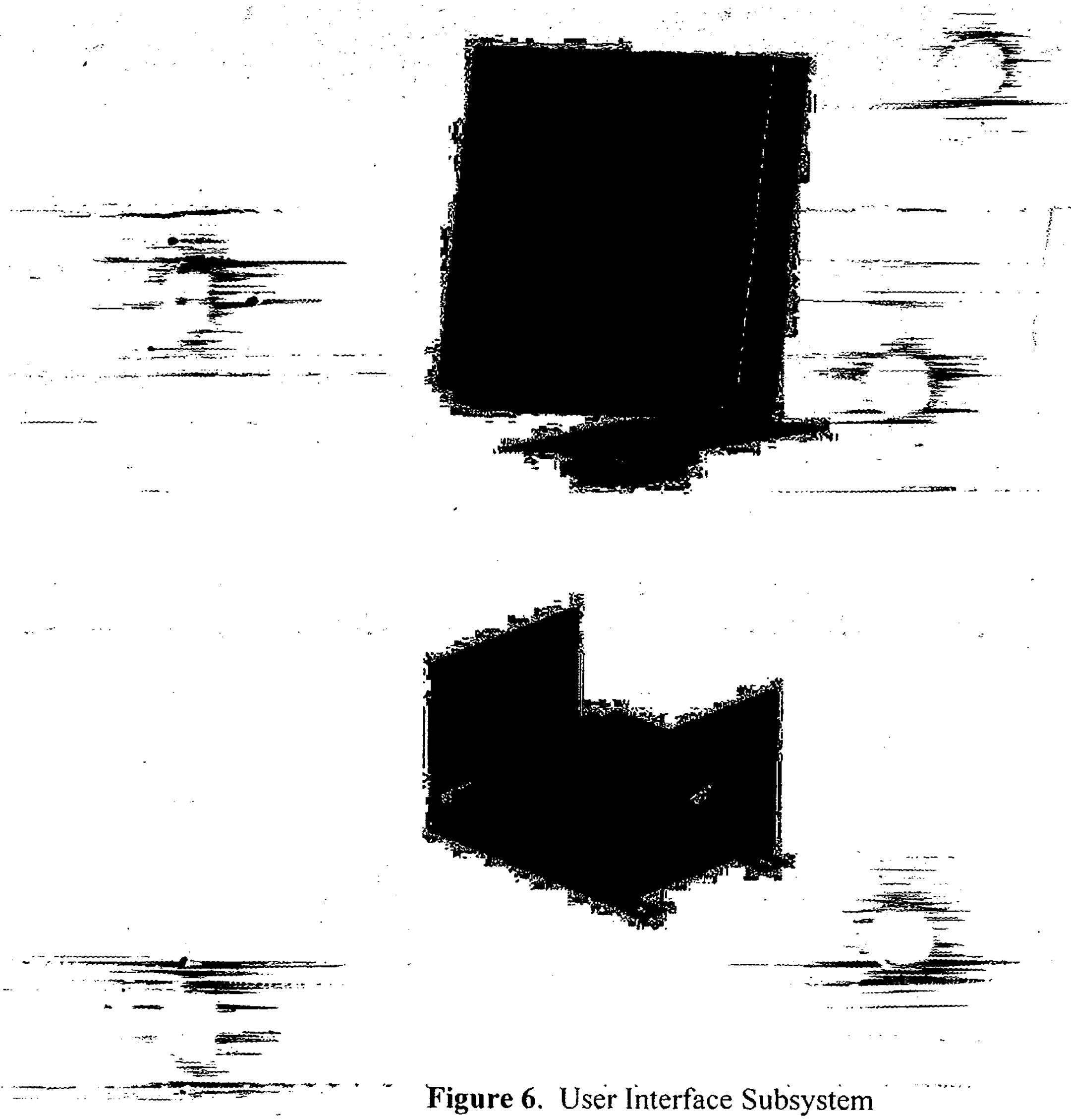

Figure 6. User Interface Subsystem

The User Interface is an electronic assembly consisting of a personal computer (PC) based main circuit board (CPU), Analog and Digital I/O peripheral circuit boards, and a color touch screen Liquid Crystal Display (LCD). The main CPU and peripheral circuit boards are mounted in an independent enclosure within the system main enclosure. The touch screen LCD is mounted on top of the main enclosure. [redacted]

[redacted]

PC-based main circuit board: [redacted] This board communicates serially with four subsystems (AOCS, Blood Pump, Bubble Detector, and User Interface) and sends/receives digital signals to/from the Safety Interlock.

Peripheral circuit boards: [redacted] expansion boards provide additional functionality, analog-to-digital conversion and digital input/output capability. The User Interface application software uses these functions.

Touch screen Liquid Crystal Display (LCD): An LCD monitor displays the video output of the PC-based main circuit board. A touch screen provides the input for user selection of application software with virtual keys displayed on the LCD.

4.1.6 Oxygen Supply Subsystem

The Oxygen Supply Subsystem (Oxygen Supply) controls oxygen gas flow to the AOCS. The Oxygen Supply has no electronic components. All oxygen-contact components have been selected for oxygen service, are cleaned for oxygen service and are rated for operating pressures. A schematic of the Oxygen Supply is shown in **Figure 7.**

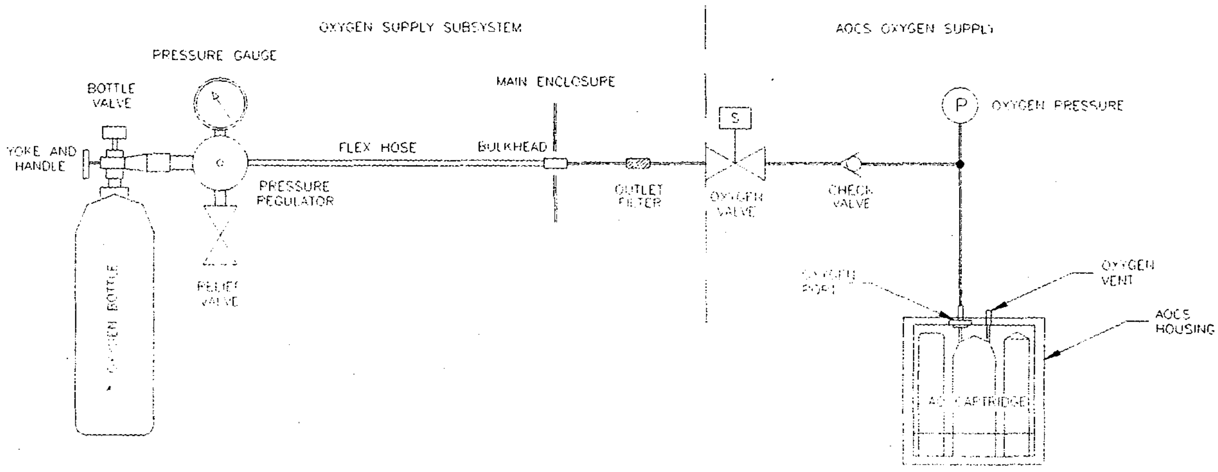

Figure 7. Oxygen Supply Subsystem Schematic

The Oxygen Supply has a standard yoke-type CGA-840 fitting, which connects to the hospital-provided oxygen bottle (E-bottle). One full E-bottle contains sufficient oxygen to support more than 50 AO Therapy procedures. The yoke is connected to a brass pressure regulator manufactured by [redacted] A pressure gauge on the regulator inlet side measures the oxygen bottle pressure; the bottle pressure must be greater than or equal to [redacted] in order to initiate AO Therapy. The regulator is protected from particulate debris by an inlet filter. The single-stage pressure regulator is pre-set at [redacted] (no user adjustment is necessary). The regulator is locked so that adjustments cannot be made to the pressure setting without a tool. A relief valve set to [redacted] is mounted on the regulator to protect the outlet side from regulator failure. The regulator outlet attaches to a Teflon®-lined metal flex-hose. The hose connects to a bulkhead fitting where the Oxygen Supply enters the system main enclosure. An in-line filter inside of the main enclosure protects components downstream of field service connections (bulkhead fitting). The Oxygen Supply connects to the Oxygen Valve on the AOCS with a 1/16" tube. Approximately 4 L of oxygen gas (STP) is necessary to pressurize the cartridge, and less than 3 ml (STP)/min is needed during AO Therapy administration.

4.1.7 Power Supply Subsystem

The Power Supply Subsystem (Power Supply) is an electronic assembly that provides DC power to the subsystems within the AO System. The Power Supply receives power from the AC Mains or internal batteries. [redacted] The isolation transformer provides electrical isolation for patient/operator protection. Batteries are incorporated for backup power and system mobility. These batteries provide a minimum of one hour of operation when fully charged. When connected to AC Mains, the system automatically charges the batteries. The Power Supply Subsystem also includes specific DC power supplies that provide fixed voltages to other subsystems.

The Power Supply Subsystem is shown installed on the system base in **Figure 8** (sheet metal enclosure removed for clarity).

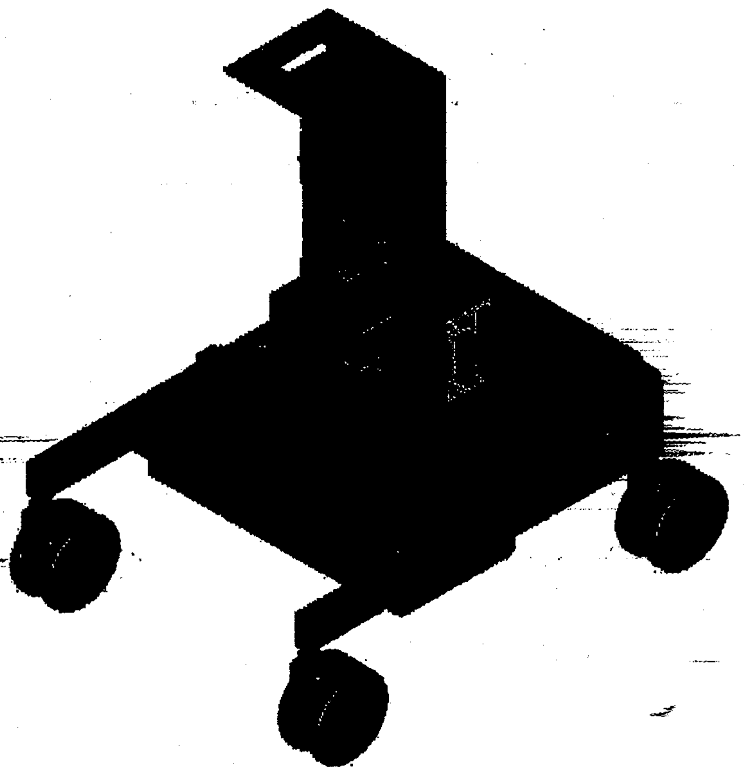

Figure 8. Power Supply Subsystem

4.2 AO Cartridge

The AO Cartridge is a sterile, single-use device that is inserted in the AO System during set-up to support AO Therapy. The cartridge creates Aqueous Oxygen (AO) solution from hospital-supplied saline and oxygen gas. The cartridge provides the blood path (tubing) that draws arterial blood from the patient and returns hyperoxemic blood to the infusion catheter for delivery to the patient. The cartridge also contains a chamber where the AO solution is delivered and mixed with arterial blood to form hyperoxemic blood. The cartridge weighs less than one pound and is primarily constructed from injection-molded polycarbonate; the tubing material is polyvinyl chloride (PVC). The cartridge is individually packaged and has a three-year shelf life. The AO Cartridge is shown in **Figure 9**.

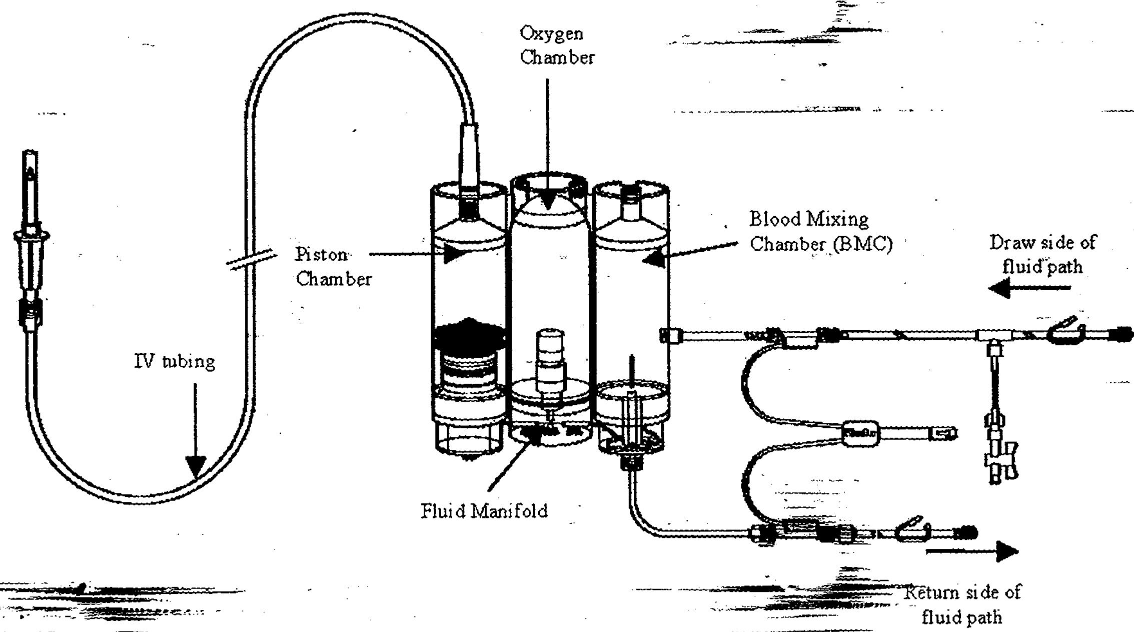

Figure 9. AO Cartridge

As shown in the figure, the AO Cartridge has three separate chambers and a fluid manifold. These chambers are the Piston Chamber, Oxygen Chamber, and Blood-Mixing Chamber (BMC). The Fluid Manifold connects the three chambers. The IV tubing on the inlet of the Piston Chamber connects directly to an IV saline bag provided by the hospital. The Oxygen Chamber inlet connects to the Oxygen Supply of the AO System. The draw tubing connects the BMC to an arterial draw sheath (arterial blood from the patient), and the return tubing connects the BMC to the infusion catheter. **Figure 10** depicts the fluid flow paths through the cartridge and the fluid flow control features.

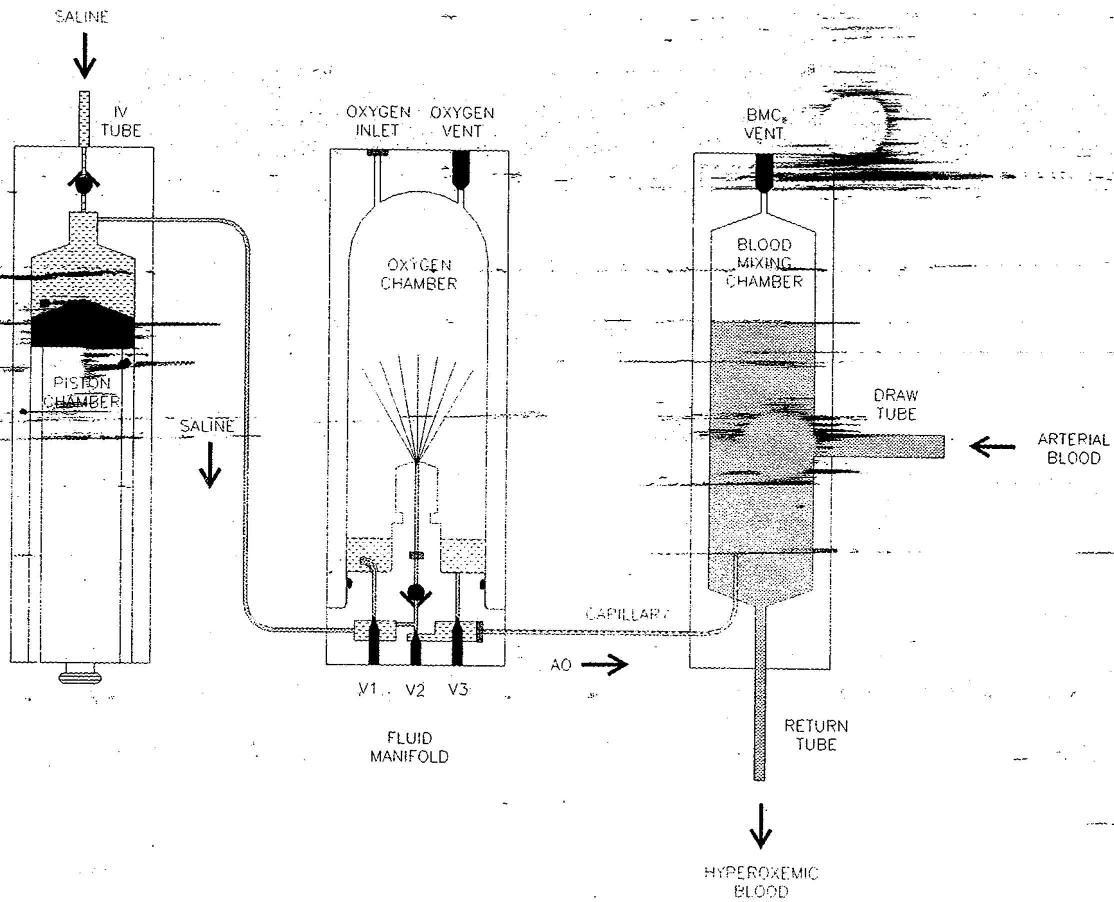

Figure10. AO Cartridge Fluid Schematic

4.2.1 AO Cartridge Features

IV Tubing and Piston Chamber: The Piston Chamber operates as a syringe pump. The piston mechanically engages the AOCS piston actuator during cartridge installation. The piston draws saline supplied from an IV bag on the downstroke, then pressurizes and pushes the liquid out to the Fluid Manifold on the upstroke. The system user connects the IV bag to the Piston Chamber IV tubing with a bag-piercing device (spike) on the tubing. A check valve in the inlet to the Piston Chamber prevents backflow of liquid to the IV bag when the chamber is pressurized (piston upstroke). A small tube at the outlet of the Piston Chamber connects to the Fluid Manifold. The Fluid Manifold prevents backflow of liquid to the Piston Chamber when the chamber is depressurized (piston downstroke). The piston provides 3 ml of saline per stroke (approximately one stroke per minute) during AO Therapy.

Oxygen Chamber: The Oxygen Chamber contains pressurized oxygen regulated to [redacted] by the AO System Oxygen Supply. The Oxygen Chamber has an inlet that seals against the AO Cartridge Subsystem (AOCS) oxygen port when a cartridge is installed in the AOCS housing. The oxygen inlet has a 0.2-µm filter. The Oxygen Chamber also has a vent valve, which is controlled by the AOCS. Pressure inside the oxygen chamber opens the oxygen vent valve when the AOCS actuator is retracted.

Fluid Manifold: The Fluid Manifold directs saline and AO solution flow through the three chambers of the cartridge as shown in **Figure 10**. The Fluid Manifold is operated to mix the necessary proportions of normal saline and AO solution in order to achieve the required concentration of dissolved oxygen for AO Therapy. The Fluid Manifold has one inlet from the Piston Chamber and one outlet to the capillary. The Fluid Manifold has three ports communicating to the Oxygen Chamber: a dilution port inlet, a nozzle inlet, and an outlet from the AO reservoir. [redacted] The AO solution collected in the AO reservoir is a mixture of oxygenated and non-oxygenated saline. The relative amounts of oxygenated and non-oxygenated saline are controlled in order to achieve the desired oxygen concentration of the effluent. AO solution exits the reservoir to the capillary outlet. The oxygen gas pressure provides the driving force for fluid flow.

The Fluid Manifold controls the fluid path with three needle valves and one check valve (ref. **Figure 10**). The dilution valve (V1) controls the entrance to the dilution port. The flush valve (V2) allows the piston chamber to deliver saline directly to the capillary. The AO flow valve (V3) controls the flow of AO solution from the AO reservoir to the capillary. The check valve allows forward flow to the nozzle, but automatically closes when the piston moves downward, allowing the Piston Chamber to be filled from the saline bag.

The Fluid Manifold seals to the Oxygen Chamber with an [redacted]. Upon system set-up, vertical clearance between the AO Cartridge and the AOCS housing permits the system user to insert the cartridge. When the Oxygen Chamber is pressurized, the Fluid Manifold pushes downward and closes this vertical clearance. This action locks the AO Cartridge in place for control of the piston and full engagement of all valves to their respective valve actuators in the AOCS. Pressure inside the Oxygen Chamber also opens the needle valves and oxygen vent valve when the AOCS actuators are retracted.

Capillary: The capillary [redacted] delivers AO solution to the blood-mixing chamber (BMC) at a rate of approximately 3.0 ml/min. The inlet to the capillary has a 2-µm filter frit protecting the capillary from possible particulate contamination. The capillary delivers the AO solution from the Oxygen Chamber into the BMC in a continuous, controlled manner that maintains the oxygen in a solubilized state. The design features developed to control the mixing and delivery of supersaturated oxygen solutions ensure that this process does not generate gas emboli.[14,15]

Blood Mixing Chamber (BMC): The BMC mixes AO solution with the patient's normoxic arterial blood to create hyperoxemic blood. Arterial blood pumped from the patient via the draw tubing enters the BMC through a tangential inlet, [redacted] This swirling flow provides controlled mixing of the inflowing arterial blood with the inflowing AO solution from the capillary, resulting in a uniform oxygen concentration. After mixing, the resultant hyperoxemic blood flow has a pO_2 level between 760 - 1000 mmHg. The hyperoxemic blood flows out of the bottom of the BMC into the return tubing.

The BMC has a vent valve that is used to establish the proper level in the BMC for mixing blood and AO solution. Pressure inside the BMC opens the vent valve when the actuator is retracted. The BMC, which has a finite liquid level height and a substantial fraction of trapped air at the top of the chamber, provides a gas trap for bubbles introduced into the draw tubing. This compressible air cushion at the top of the chamber also acts as a pulse dampener for the peristaltic pump.

Draw Tubing and Return Tubing (Blood Path): The blood path has 1/8" I.D. draw tubing that is sized to fit the Blood Pump head and provide minimal pressure drop upstream of the pump head. The system user loads the draw tubing into the pump head and draw tubing clamp during set-up. The draw tubing also has a sample port for withdrawing blood samples for systemic arterial pO_2 measurement.

The blood path has 3/32" I.D. return tubing is sized to fit into the flow and bubble detector probes. The user loads the return tubing into the bubble detector probe, flow probe, and return tubing clamp during set-up. The draw and return tubing ends (with luer fittings) are in a sterile pouch and are handed to the physician in the sterile field during set-up.

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[14] Brereton GJ *et al.* (1998). Nucleation in Small Capillary Tubes. *Chemical Phys* **230**:253 – 265.
[15] Creech JL *et al.* (2002). Injection of Highly Supersaturated Oxygen Solutions without Nucleation. *J Biomech Eng* **124**:676 – 683.

AO Cartridge Pressure Transducer Assembly: Both the draw and return tubes are equipped with in-line disposable pressure transducers. These pressure transducers are supplied by [redacted] The two pressure transducers, an Electrically Programmable (Add-Only type) Read Only Memory (EPROM) device, and a cable with a modular connector form the AO Cartridge Pressure Transducer Assembly. The modular connector of the assembly interfaces with a modular jack on the front of the AO System. During use, the AO System writes to the EPROM, which prevents reuse of the cartridge.

4.3 [redacted] Infusion Catheter

The ML-Cath catheter is a sterile, single-use over-the-wire device that may be inserted into patients through commercially available guide catheters 6 F or larger. The catheter's outer diameter (O.D.) is 4.6 F from the distal tip to the proximal strain relief. The polyethylene catheter body is extruded in a continuous process that transitions from soft tip to the stiffer proximal shaft. The inner lumen is smooth and free of transitions, and the catheter has a single end hole for fluid exit. The usable length is 127 cm and the overall length of the catheter is 135 cm. The inner diameter (I.D.) of the catheter is nominally 0.046 in except at the location of the platinum/ iridium radiopaque marker band. The I.D. under the marker band is a minimum 0.037 in. The catheter is individually packaged and has a three-year shelf life. The [redacted] catheter is shown in **Figure 11.**

4.3.1 [redacted] Features

Luer Hub: A female luer hub is molded over the proximal O.D. of the shaft. The luer hub enables attachment of the AO Cartridge return tubing to the catheter.

Strain Relief: A polyolefin strain relief is applied over the shaft and luer hub joint with a heat shrinking process.

Proximal Shaft: The catheter has a non-plasticized white high-density polyethylene (HDPE) proximal shaft.

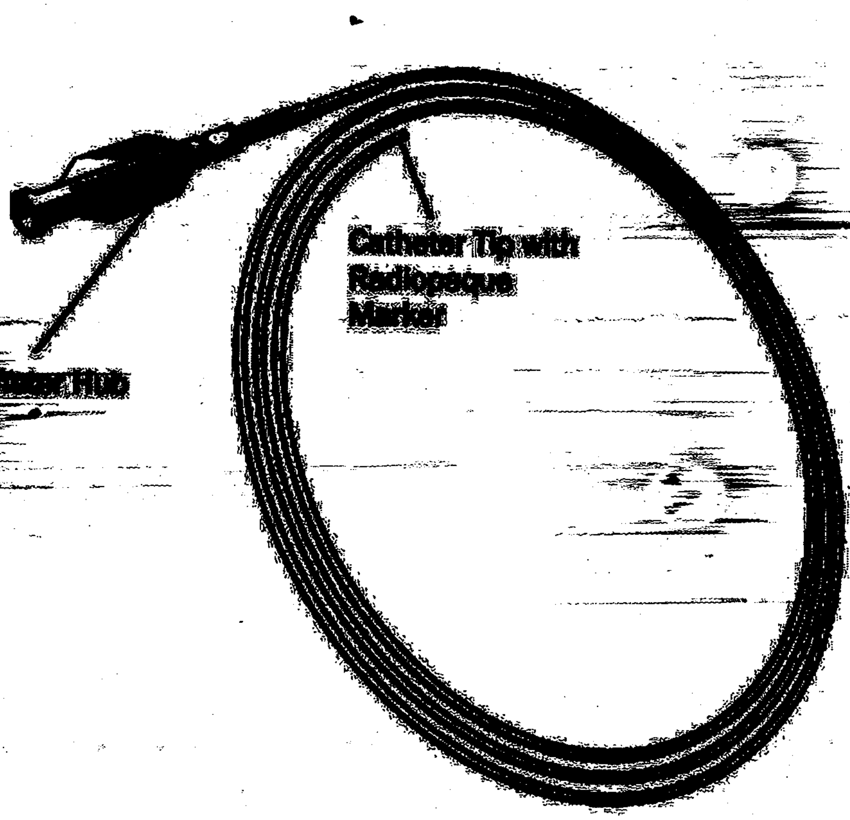

Figure 11. [redacted] Infusion Catheter

Distal Tip: From the distal tip termination to a nominal distance of 18 cm, the distal tip material is a flexible low-density polyethylene (LDPE) plasticized with 4% ethylene vinyl acetate (EVA). The distal tip has a smooth radius to reduce the potential for vascular injury.

Radiopaque Marker Band: The radiopaque platinum/iridium alloy marker band is used to visualize the catheter fluoroscopically during use and is fitted within 0.2 cm of distal tip termination.

4.3.2 Patient Connections

The AO Cartridge draw tubing connects to the sidearm of the same femoral arterial sheath that may be used for angioplasty and stenting procedures. Sheath placement may be coaxial (in one femoral artery) or contralateral (in both the right and left femoral arteries), at the physician's discretion. The preferred coaxial configuration, shown in **Figure 12**, illustrates how arterial blood is withdrawn via the sidearm through the annular space between the guide catheter and sheath; in this configuration, a single 8F introducer sheath can be used. The AO Cartridge draw tubing luer fitting connects to the sidearm. The [redacted] catheter is placed through the 6F guide catheter over a guidewire, to the desired target location within a coronary artery. The guidewire is removed prior to initiation of blood flow. When extracorporeal blood flow is [redacted] catheter and AO Cartridge return tubing are wet-connected to ensure that no gaseous emboli are introduced to the patient during priming. The term 'wet connection' requires that both devices are fully blood-primed and free of trapped air bubbles. The cartridge return tubing luer fitting connects to the luer hub of the [redacted] catheter. For the contralateral approach (not shown), a 5F introducer sheath is used on the draw side, while a 6F introducer sheath provides access for the 6F guide catheter. This alternative approach may be used by physicians who prefer to use two smaller sheaths for arterial access (5F and 6F) instead of a single 8F sheath.

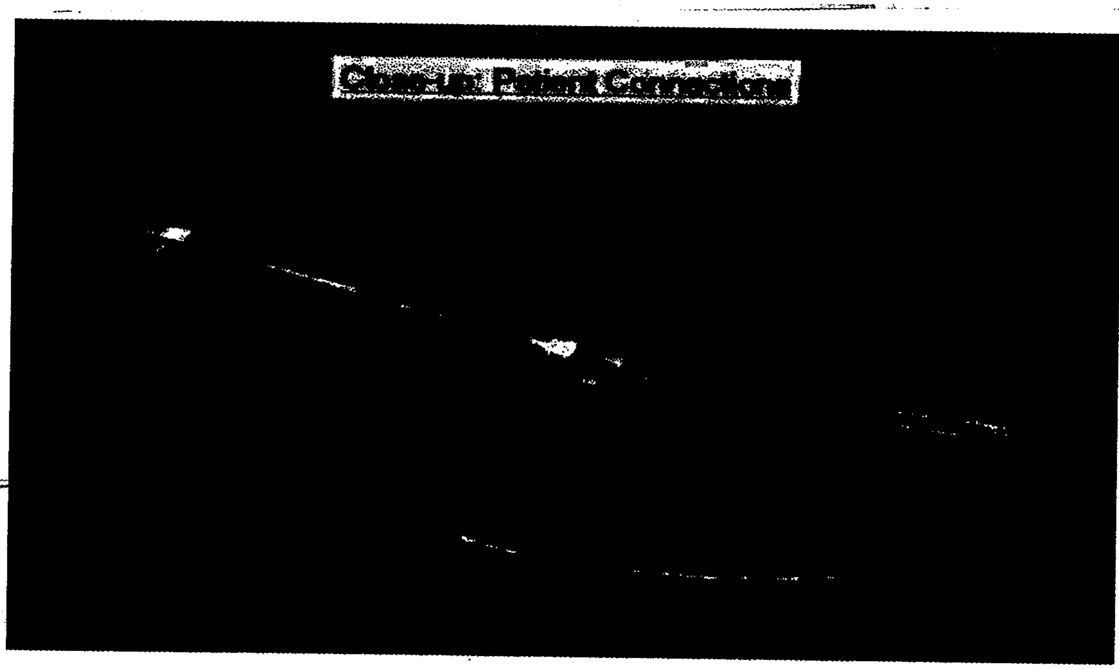

Figure 12. Co-axial Draw/Return Clinical Configuration for AO Therapy

5 Principles of Operation

The AO System is operated by a trained health care professional (user). Treatment is initiated in the [redacted] The User Interface guides the health care professional (user) through setup and clinical operation. The operating principles for AO Therapy are provided herein. Two distinct processes are combined to perform AO Therapy. These processes occur within an extracorporeal (EC) circuit, which is controlled by the AO System. The first process is AO solution delivery; the second process is extracorporeal blood circulation. The AO System controls and monitors these processes for safety.

A block diagram of the AO System shown in **Figure 13** identifies the interaction of the AO System with the AO Cartridge, and the integration of subsystems within the AO System. The AO Cartridge is functionally split into an AO solution delivery side, which interacts with the AOCS; and the blood circulation side, which interacts with the Blood Pump, Bubble Detector, and Safety Interlock.

5.1 AO Delivery Process

During AO Therapy, AO solution is produced in the AO Cartridge and delivered through the capillary into the BMC at a rate of 3 ml/min for ninety minutes. The AO concentration is set to achieve blood pO_2 levels ranging from 760 to 1,000 mmHg using patient arterial blood. When the blood path is primed but AO solution is not being delivered, the AOCS maintains a saline flush through the capillary.

Cartridge Preparation (Prep): After the AO Cartridge has been loaded into the AOCS and the user has spiked the bag, the user can Prep the cartridge. The purpose of Prep is to saline prime the fluid path in the high-pressure side of the cartridge, establish the minimum liquid level, and pressurize with oxygen. Prep is fully automated after user initiation. The AOCS piston actuator drives the cartridge piston upward to expel the air in the piston chamber and until it reaches the top of stroke (max travel sensor). The piston reverses direction and pulls the piston downward to draw liquid from the saline bag, stopping at the bottom of stroke (home sensor). The piston up/down cycles continue until liquid is pushed from the piston chamber into the oxygen chamber. Once the AO Low level sensor detects the liquid level in the oxygen chamber, the AO System interrupts the sequence. The AOCS returns the piston to the home position, verifies AO level, and then pressurizes the oxygen chamber from the oxygen supply system. Once oxygen pressure exceeds a low-pressure threshold (approximately [redacted] and the piston returns to the home position, Prep is completed.

[redacted]

[redacted]

AO Delivery: The AOCS monitors AO solution level within the AO Cartridge Oxygen Chamber. The AO solution low level sensor detects low level when the AO solution reservoir volume decreases to 5 ml. Detection of low level initiates a fill cycle. The fill cycle starts when the piston actuator drives the piston upward to build pressure in the piston chamber. After the load cell signal reaches a hardware threshold (approximately [redacted]), the piston begins to deliver saline to the Oxygen Chamber. The delivered saline volume is set to 3 ml by commanding the piston stepper motor to turn 50 revolutions after the hardware threshold has been reached. The AO flow needle valve remains open throughout the fill cycle, maintaining a constant AO solution flow rate. The fill cycle occurs approximately once every minute during AO solution delivery.

The AO System controls the AO solution oxygen concentration. [redacted]

When the piston returns home, the needle valve remains closed and the check valve closes, allowing the piston to draw saline from the IV bag into the Piston Chamber. The AOCS software uses measured system temperature, oxygen pressure, AO solution flow rate, blood flow rate, and the patient's arterial pO_2 range setting to determine the desired AO concentration and [redacted] This determination is made at the start of each fill cycle.

Capillary Flush: The purpose of the capillary flush is to prevent blood from entering into the capillary when blood is in the BMC but AO solution is not flowing. The flush is accomplished by a repeating flush cycle. The cycle starts when the piston actuator drives the piston upward to build pressure in the Piston Chamber until the piston load cell reaches a hardware threshold (approximately [redacted] After the threshold is reached, the piston stops and the flush needle valve opens, allowing saline from the Piston Chamber to flow through the capillary. The flush needle valve closes, and the piston returns to the home position. After the piston returns home, another flush cycle starts. [redacted]

5.2 Blood Circulation Process

The process of blood circulation through the AO Cartridge is similar to other extracorporeal blood circuits, although the blood flow rate and blood contact surface area are significantly lower than other applications (*e.g.*, cardiac bypass). During AO Therapy administration, arterial blood from the patient circulates through the extracorporeal circuit comprised of the AO Cartridge draw tubing, Blood Mixing Chamber (BMC), return tubing, and the [redacted] infusion catheter. The AO System circulates arterial blood using the peristaltic Blood Pump.

During AO Therapy, the BMC combines 72 ml/min inflowing arterial blood with approximately 3 ml/min of AO solution to create 75 ml/min of hyperoxemic blood with a pO_2 between 760 – 1000 mmHg. Hyperoxemic blood is returned to the patient through the infusion catheter.

Blood Path Priming: Prior to Prime, the AO Cartridge has been prepped for AO delivery, the Infusion Catheter has been placed by the physician into the target coronary artery, and the physician has connected the AO Cartridge draw tubing to the sidearm of the arterial draw sheath. Priming the extracorporeal circuit requires two health care professionals; the user operates the system while the physician performs a wet connection between the return tubing and the infusion catheter after both devices are blood-primed.

Blood priming is initiated when the user presses and holds the prime switch. This action opens the draw tubing clamp and starts the Blood Pump. The Blood Pump head [redacted] generating a return blood flow rate of approximately 75 ml/min. When the BMC low-level sensor detects blood level, the BMC vent closes and the return tubing clamp opens.

Prior to wet-to-wet connection with the Infusion Catheter, both the system user and the physician operator confirm that blood priming of the return tubing is complete. Priming is completed after wet-to-wet connection when the blood flow rate measured by the flow probe exceeds 50 ml/min, and the Bubble Detector has adequate signal strength. The priming volume of the extracorporeal circuit is approximately 60 ml.

Blood Circulation: After blood priming, the AO System circulates blood at a flow rate of 75 ml/min using a peristaltic Blood Pump. Once Prime has been completed, the Blood Pump changes from a constant output [redacted] to flow control mode with feedback from the flow probe. Flow measurement feedback is used to adjust pump speed so that the flow probe measurement is maintained at 75 ml/min. Normoxic arterial blood is pumped through the extracorporeal circuit until the user initiates AO solution flow via the User Interface. During this initial period, before AO solution flow is started, saline is flushed through the capillary into the circuit.

After AO solution delivery has been initiated, hyperoxemic blood is returned to the patient at blood flow rate of 75 ml/min. After 90 minutes of treatment, the flow of AO solution is discontinued while normoxic blood continues to circulate until the user ends the procedure.

6 AO Therapy Safety

The AO System monitors operating parameters to detect and respond to unsafe conditions. When an unsafe condition is detected, the AO System stops treatment and isolates the extracorporeal circuit from the patient. The safety processes described here address potential unsafe conditions that have been identified for the AO solution delivery and blood circulation processes, as well as general medical electrical equipment operation. These safety processes were designed using a comprehensive risk-based approach.

AO Delivery safety monitoring: Safety monitoring for AO solution delivery includes detection of overpressure in the Piston Chamber and in the Oxygen Chamber. The cartridge operates with a maximum piston pressure of [redacted] The hardware threshold for piston overpressure is set to [redacted], well below the failure limit for the device. As a redundant protection against piston overpressure, the stepper motor encoder will stop AO solution production if a motor stall is detected; thus, the potential for motor failure is monitored as well.

The operating range for pressure in the Oxygen Chamber is [redacted] The hardware threshold for overpressure of the Oxygen Chamber is set to [redacted] well below the failure limit for the device.

Blood Circulation safety monitoring: Safety monitoring for blood circulation through the AO Cartridge is similar to other extracorporeal blood circuits, such as hemodialysis machines. The Bubble Detector continuously monitors the blood path after the system has been primed. The system will not complete the Prime sequence if the Bubble Detector transducer is not properly loaded. The Bubble Detector detects individual bubbles with diameter $\geq$ 100 μm, and quantifies the cumulative bubble volume during AO Therapy. The Bubble Detector also monitors signal strength, ensuring the return tubing is properly loaded in the bubble detector probe. If the cumulative bubble volume reaches 10 μl during the 90-minute treatment, or signal strength is out of range, the Bubble Detector initiates a system shutdown. The AO System monitors the level of blood in the BMC during treatment and initiates a system shutdown if the level is excessively high or low.

Safety systems for blood circulation include detection of high pressure on the return tubing or low pressure (suction) on the draw tubing. Two disposable transducers in the tubing set of the AO Cartridge measure pressure. The threshold for BMC pressure is set to [redacted]; this pressure is the maximum in the circuit because the BMC is located immediately after the output side of the Blood Pump. The threshold for negative draw pressure is – 300 mmHg [redacted]

The Blood Pump head is fully occlusive and can isolate the draw tubing from the BMC at the stop threshold of [redacted] The return tubing clamp also isolates the return tubing from the BMC at this level.

The Blood Pump has an encoder on the servomotor to verify pump speed. If the pump speed is out of range (high or low), or the motor stalls, the encoder detects the fault condition. The Blood Pump is unidirectional, so blood cannot be pumped back to the patient through the draw tubing. The pump head detector also senses if the pump head is opened during operation. Opening the pump head while blood is circulating generates a fault condition.

The AOCS monitors the blood level height in the BMC during treatment. The BMC low-level sensor threshold is set at the minimum blood level at which blood and AO solution can mix effectively. This sensor protects against either the gradual accumulation of bubbles in the BMC or the sudden introduction of air or oxygen into the BMC. The BMC vent is always open when minimum blood level is not detected. Thus, any sudden introduction of gas into the chamber will be vented out.

The BMC high-level sensor monitors the presence of the gas headspace (gas trap) in the top of the BMC. If this headspace decreases due to excess pressure or a vent valve leak, the BMC high-level sensor detects a fault condition.

AO System Safety Response: If an unsafe condition is detected, a system shutdown occurs: the Blood Pump stops and the draw and return tubing lines are isolated from the patient by two automatically-operated tubing clamps that are mounted on the AO System. In the event of a system shutdown, the cartridge is depressurized and is unloaded manually. A new cartridge must be loaded to continue treatment.

Fault conditions include over pressure, motor stall, BMC Low, other AOCS fault conditions, or a fault condition from the Safety Interlock. Safety Interlock fault conditions include Bubble Detector signal threshold, cumulative bubble volume, high BMC pressure, excessively negative draw pressure, high or low blood flow rate, high or low BMC level, or another fault condition from the Safety Interlock or User Interface. If the cumulative bubble volume reaches 10 µl during the 90-minute treatment, or signal strength is out of range, the Bubble Detector shuts down the system via the Safety Interlock.

All AOCS valves are normally closed, so they isolate in event of a power loss. The AO Cartridge oxygen vent valve also acts as a relief valve in the case of overpressurization. If piston or oxygen overpressure is detected, the oxygen vent valve will automatically open to release pressure. In addition, if BMC low is detected, the BMC vent valve automatically opens. Gas cannot flow into the return tubing when the BMC vent valve is open.

7 Operating Sequence

The AO System has three operating modes: Normal, Demo, and Diagnostic. The Demo and Diagnostic modes are for training or field service respectively, and can only be entered with the use of a specific hardware device under the control of TherOx personnel. The principles of operation are described with the system in Normal operating mode.

In normal operating mode, the AO System is located in the catheter lab with the patient, who has completed PCI with stenting post-AMI. Two users are required to operate the system. A first user (user) installs the AO Cartridge and operates the AO System during the 90-min treatment. A second user (physician) places the infusion catheter, performs the tubing-to-catheter wet connection, and is present when AO Therapy is set-up and initiated.

Prior to set-up, the user opens the oxygen bottle and checks that the bottle pressure is greater than [redacted] (if not, the hospital exchanges the E-bottle). The user hangs the hospital-provided saline solution bag on the IV pole, plugs the system into a power outlet, and turns the system on.

Once the system is turned on, the user is trained to perform a sequence of steps, which are defined in the Instructions for Use and Operation Manual. Equipment operation during AO Therapy is serial; as steps are performed, the AO System touch screen LCD (display) instructs the user on the next step. These steps are presented in the AO System operation flow chart, **Figure 14**. System operation is explained within specific system operating sequences: Load, Prep, Prime, AO Off, AO On, End Procedure, and Unload. In order to start AO On and initiate hyperoxemic reperfusion, each of the previous steps has to have been completed. The user can end the procedure and unload the AO Cartridge at any step in the sequence and at any time during AO Therapy.

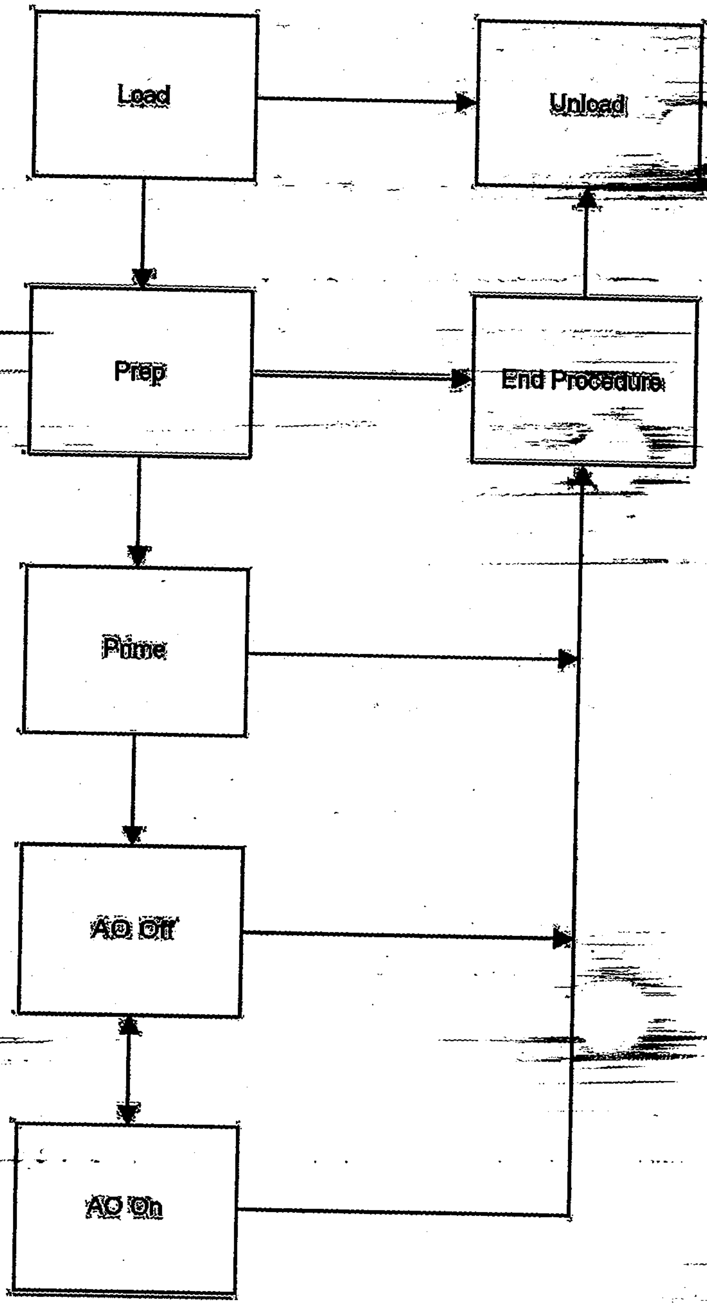

Figure 14. AO System Operating Sequence

Load Sequence: The user removes the AO Cartridge from the sterile pouch, and presses the "Load" virtual key on the display. The user opens the AOCS door, inserts the cartridge, and then closes the door. After the AOCS detects that the cartridge is present and the door is closed, the "Prep" screen appears on the display. The user inserts the IV inlet spike into the saline bag. The user installs the draw tubing into the pump head and tubing clamp, and installs the return tubing into the bubble detector probe, flow probe, and return tubing clamp.

The AO Cartridge tubing end connections (contained in a sterile pouch) are handed to the physician, who is in the sterile field. The user inserts the modular transducer connector into the transducer jack. After the connector is inserted, the AO System is ready to Prep the cartridge.

Prep Sequence: The user presses the "Prep" virtual key on the display to start the Prep sequence. When Prep is complete (after approximately 3.5 minutes), the User Interface display changes to the "Prime" screen and the system waits for the Prime sequence to be initiated.

Prime Sequence: The Prime sequence requires two users; one user operates the AO System, while the physician connects the AO Cartridge return tubing to the infusion catheter. The infusion catheter has been placed into the target artery prior to priming and the guidewire has been removed. Prime sequence is initiated from a hardware switch that the user is required to press and hold. While the user is pressing the prime switch, the physician is preparing to make the wet connection to the infusion catheter. Both users can observe the blood priming prior to making a wet connection with the catheter.

After the blood path is primed, the physician makes the wet-to-wet connection. The AO System remains in the Prime sequence until the minimum measured blood flow rate of 50 ml/min is achieved: the LCD display changes to the "AO Off" screen and the user releases the Prime switch.

AO Off Sequence: In "AO Off", the AO System continuously circulates patient blood at a constant rate of 75 ml/min, and flushes the capillary with saline. This sequence is initiated automatically after the Prime sequence is completed. The "AO Off" display screen has a virtual key to start "AO On". The user selects the appropriate patient systemic arterial pO_2 range (based on a measured patient arterial blood sample) by pushing up/down virtual keys on the "AO Off" screen. The system will not initiate "AO On" until an arterial pO_2 range is selected.

AO On Sequence: The user initiates the "AO On" sequence by pressing a virtual key on the "AO Off" screen after a pO_2 range has been selected. In "AO On", the AO System continuously circulates patient blood and infuses AO solution at a constant rate. The hyperoxemic return blood flow rate is maintained at 75 ml/min. The AO flow needle valve remains continuously open during "AO On", delivering 3 ml/min. The AO System maintains the AO solution reservoir level and controls the AO concentration during operation.

The "AO On" display screen has a virtual key to return to "AO Off", and has up/down virtual keys to adjust the arterial pO_2 range setting. The user is instructed to measure the patient's arterial pO_2 at 30-minute intervals and adjust the range setting if necessary. A timer displays the running "AO On" (treatment) time in minutes. At the end of 90 minutes of "AO On", the AO System returns automatically to "AO Off" and prompts the user to End Procedure.

End Procedure: When the user presses the virtual End Procedure key on the display, blood flow is stopped and the tubing clamps close. The AO System displays the "Unload" screen. When the virtual "Unload" key is pressed, the oxygen vent opens and depressurizes the Oxygen Chamber. When the oxygen pressure is below 10 psig, all needle and vent actuators open, and the door unlocks for manual cartridge removal. The physician also removes the infusion catheter and guide catheter at this time.

TherOx recommends that the AO Cartridge be disposed of without attempting to return the priming volume of 60 ml blood to the patient. The catheters and access sheath are removed per standard interventional procedures for the cardiac catheterization laboratory.

8 Glossary

Aqueous Oxygen or "AO" Solution

Oxygen gas is dissolved in physiologic saline under high pressure to create a highly oxygenated solution called "Aqueous Oxygen" or "AO" solution.

TherOx® Downstream AO Cartridge or "AO Cartridge"

The AO Cartridge is a sterile, single-use disposable medical device. The cartridge has a three-chambered main body wherein AO solution is created and mixed with the patient's arterial blood. Draw tubing enables withdrawal of the patient's arterial blood, and return tubing attaches to an infusion catheter to return the oxygen-enriched hyperoxemic blood back to the patient.

TherOx® Downstream AO System or "AO System"

The AO System is a re-usable mobile hardware unit that houses and operates the AO Cartridge. The AO System controls and monitors performance and safety during the administration of AO Therapy.

AO Therapy

AO Therapy refers to the procedure of withdrawing the patient's arterial blood, mixing it with highly oxygenated AO solution, and returning the oxygen-enriched hyperoxemic blood back to the patient's coronary arteries after AMI. AO Therapy is performed with the AO System and AO Cartridge.

hyperbaric

Hyperbaric denotes greater than atmospheric pressure. Within the AO Cartridge, AO solution is created at hyperbaric oxygen gas pressures.

hyperoxemic blood

Blood that is oxygenated to greater-than-physiologic levels is described as hyperoxemic. The AO Cartridge mixes the patient's normoxemic arterial blood with AO solution to create hyperoxemic blood that has a pO_2 range of 760 – 1000 mmHg. Hyperoxemic blood is returned to the coronary arteries during administration of AO Therapy.